A STUDY OF CARDIOVASCULAR AUTONOMIC FUNCTION IN NORMOTENSIVE HYPERTENSIVE SUBJECTS

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CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY OF CARDIOVASCULAR AUTONOMIC FUNCTION IN NORMOTENSIVE HYPERTENSIVE SUBJECTS"** is the bonafide original work of **Dr. K. MURALI KRISHNAN** in partial fulfillment of the requirements for **M.D. (PHYSIOLOGY) BRANCH – V** Examination of the Tamilnadu Dr. M.G.R. Medical University to be held in March 2007. The period of study was from February 2005 to March 2006.

Dr. D.R. GUNASEKARAN, M.S.
DEAN
Govt. Stanley Medical College &
Hospital,
Chennai-600 001.

Dr. K. BALASUBRAMANIAN, M.D.
Professor & Head
Department of Physiology
Govt. Stanley Medical College
Chennai-600 001.

DECLARATION

I, **Dr. K. MURALI KRISHNAN,** solemnly declare that dissertation titled, "**A STUDY OF CARDIOVASCULAR AUTONOMIC FUNCTION IN NORMOTENSIVE HYPERTENSIVE SUBJECTS"** is a bonafide work done by me at Govt. Stanley Medical College & Hospital during 2004-2007 under the guidance and supervision of **Dr. K. BALASUBRAMANIAN, M.D.** Professor and Head, Department of Physiology, Stanley Medical College, Chennai-600 001.

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Place : Chennai.

Date :

(Dr. K. MURALI KRISHNAN)

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INTRODUCTION

Hypertension is the most common disease – specific reason for which many visit physician. This is currently among the leading cause of mortality and morbidity in the world and is expected to have an even greater impact on the health of public as more of the world becomes developed.

In addition to these events the undetected normotensive hypertension (Stephen P. Glasser et al 2002) is a powerful risk factor that increases the individual (or) the population, who will develop wide variety of cardiovascular (CV) diseases. In the next decade more and more patients will become candidates for antihypertensive therapy. Hypertension is a sustained elevation of both systolic and diastolic Blood pressure. Essential hypertension is idiopathic and polygenic in origin and environmental factors are very much involved. Apart from few examples where single genetic basis of blood pressure regulation and its dysfunctions, essential hypertension is the sum of interactions between multiple environmental & genetic factors (Kurtz TN et al 1993). We can also recognize that the development and maintenance of hypertension may involve many systems including Cardiac, Vascular, Renal, Endocrine, and Nervous system, etc. It is to be remember that the individual is named as hypertensive, the changes have already taken place in the CVS and other systems also. Hence it is necessary to detect (or) predict **normotensive hypertensive** concept as earlier as possible (Stephen et al 2002). Even a moderate elevation of arterial pressure leads to reduced life expectancy. In most patients with essential hypertension there is a strong correlation of hereditary factors has proved beyond doubt in Okatomostrain (rats). Cardiac and vascular changes could be

considered risk factors for Cardiovascular disease rather than marker's of established disease. These Cardiovascular risk factors are the change in the autonomic nervous systems regulation, changes in lipid metabolism, obesity, insulin resistance, arterial stiffness, left ventricular hypertrophy and renal disease etc.

The changes associated with ANS plays a fundamental role in adapting the heart and circulation to be within the physiological limits.

It has been earlier accepted that baroreflex had little to do with long term control of blood pressure, but now there has been intense speculation on the role baroreflex mechanism along with a long term BP control. Recent evidence projects that arterial baroreflex mechanisms do operate in normotensive hypertensive subjects at a slightly higher level.

The two limbs of in the regulation of cardiovascular autonomic function, 1) base line autonomic level in HT and 2) is whether the normotensive HT differ in terms of blood pressure and HR responses to simple autonomic reflex test. An increase in cardiac out put (CO) or HR or both will increase the BP. Even in the case of normal peripheral resistance (PVR), the BP can increase due to above cause but comes back to normal BP level by BP regulating mechanisms. But an increase in BP alone to the increase in PVR would also be offset by a reflex decrease in CO. But this phenomenon does not happen and the increase in arterial pressure is maintained and it makes clear enough that the baroreflex mechanism reset to maintain an elevated arterial pressure. This is the essence elevated BP (Logo and Taylor 1994). Essential hypertension is an impairment of auto regulation of the tissue blood flow. This imbalance could be due to reduced vagal discharge from the Central Nervous system (CNS) (Or) increased sympathetic drive to the heart and vessels or preload increase in renal disease.

The changes in the blood pressure is also effected by renal volume restoring mechanisms which are activated by baroreflex which is an important part of ANS. Changes is the BP is also brought about by the changes in the heart rate, which is very much controlled by parasympathetic discharge. The action of ANS is the most essential limb in the regulation of blood pressure. A balance control between SNS and PNS is necessary for maintaining cardio vascular changes in rest and in stress. So any alteration in ANS can pay an important role in the etiology of hypertension.

The present study is aimed for evaluating the cardiovascular autonomic response in normotensive hypertensive subject using standard autonomic function test. In this study I have tested the recommendation of Ewings test for CVS ANF. This includes BP and HR response during supine rest, BP and HR response during quite standing (Ewings et at al 1985), HRV during deep breathing, Valsalva ratio during Valsalva maneuver, HR and BP changes during sustained isometric hand grip test (SIHG) and cold pressor test (CPT). Most of this test the baroreflex sensitivity. The most important recent method of quantifying CVS ANF is by HRV using Power spectral density (PSD) analysis in Frequency domain and time domain. The ratio between PNS and SNS is also calculated and results give clear idea about sympathovagal balance. These above test are highly sensitive, recordable, reproduciable, non-invasive and less expensive.

In the present study I have made an attempt to carry out the hypothesis of normotensive hypertensive concept by comparing the cardiovascular autonomic function variables of male offsprings of hypertensive non-diabetic with male offsprings of non-hypertensive, non-diabetic parents.

REVIEW OF LITERATURE

HISTORICAL PROSPECTIVE

- Galen 1528 – showed vagosympathetic trunk
- Etienne's Stephamis (1545) found out vagus and sympathetic nerves were separate nerves.
- Whytts (1751) – proved the essence of reflex actions.
- Weber & Weber 1845 – showed that HR is reduced by vagal stimulation; HR is increased by sympathetic stimulation.
- 1898, Langley introduced autonomic neurvous system
- WB Canon 1851 – coined the term Homeostasis and the servo control.
- Karplus 1909 – proved to the world the role of hypothalamus in the regulation of Blood pressure.
- Herring 1920 found the existence of Baroreflex activity.
- Alquist 1948 – found the receptors and sympathetic SNS.
- Hon and Lee St 1965 – Noted the fetal HR changes during fetal distress.
- Albert B Lewin (1966) – observed the changes in heart rate during Valsalva maneuver.
- Timothy wheeler 1973 – showed beat to beat variations in HR as a measure of vagal function.
- Ewings et al 1973. Isometric hard grip test as sympathetic measure and HRV analysis from short term ECG recording.

- Page and wathins 1977 devised simple orthostatic test
- Wolf et al 1977 – reduced HRV is a risk of sudden death in post Myocardial Infarction.
- Ewings & clark 1980 – found the quantitative ANFT.
- Akselord et al 1981 – Introduced spectral analysis of HRV in short term and long term ECG recording.
- Cerulli 1991 – Spectral analysis of HRV in rats.
- Zieglec D 1992 – spectral analysis of HRV in humans.
- Low et al 1995 said about Postural Orthostatic tachycardia syndrome (POTS). tolarz K et a,l, 2002 HRV-2000 in that study power spectrum analaysis of HR in young people with family history of HT shown higher LF value in lying position and less pronounded changes of HRV component after standing.
- Reudeiger H. et al have shown the PNS, SNS activation in HRV in male hypertensive subjects in mental stress.
- ES Prakash et al 2004 have studied HRV analysis and standard ANFT in different HT subject and shown that HRV deep breathing is a simple measure of vagal effects in HT, RPP provides a simple measure of overall HRV in HT.
- Jenning JR et al 2005 have studied ANF in white coat HT, where frequency domin in HRV being taken as the measure of ANF. They have shown that there is reduction in HF, greater LF/HF ratio.
- Karenyan et al 2003 have studied HT in male and followed them for 8-26 years. Their

conclusion was, life style modification is the basis for hypertension.

- Pol Merteuriusz et al 2003 have shown persistence influence of sympathetic activity, after 30mts of moderate physical exercises on HRV in patient with arterial hypertension.
- Ronnernelerh et al 2003 have shown circadian profiles of HRV time domain analysis. They found that overall HRV is diminished at night and increased during day time. As age advances the HRV decreases gradually.
- Maver JR et al 2004 have studied ANFT with normotensive subject with family history of Hypertension. Normotensive subjects with family history of hypertension showd higher resting SBP, a decrease HF band, LF is very much increased LF/HF ratio increased.
- Cybulski G et al 2003 studied influence of age on the immediate response to the active orthostatic test. There was alteration in HR during study analyzed by ECG using Liner regression model. They obtained no correlation between BMI and HR.
- Perini , veisessteims A et al 2003 studied HRV and autonomic activity at rest and during excerise in various physiological condition. The powers of HF and LF components of HRV have been shown to estimate sympatho vagal activity. HF modulation is brought by increased respiratory activity. LF nu changes are seen from lying to standing position in normalized unit (nu).
- Srinivas K and Sucharita S, et al 2002 have showed the HRV on standing in three age groups of male subject, HRV is highest in young and children. HRV was low in old age.
- Sacha, J Pluta W et al 2005 different methods of HRV analysis reveal. The type of signals that determines the sign of correlation among total power, LF and HF. The parameter

obtained from the corrected signals, normalized quantities and LF/HF reveal a consistent relationship with heart rate. parameter obtained from corrected signals, nu quantities and LF/HF ratio reversal a consistent relation ship with heart rate.

- Stolarz K et al, 2002 HRV-2000 in that study power spectrum analaysis of HR in young people with family history of HT shown higher LF value in lying position and less pronounded changes of HRV component after standing.

AUTONOMIC REGULATION OF CARDIO VASCULAR FUNCTION Autonomic nervous system through the autonomic reflex that regularly respond to internal and external stimuli modulate the activity of the body's organs. ANS is like any other somatic nervoes system, is well organized on the basis of reflex arc. This is fully seen in CVS. ANS depends on the functional integrity of multiple autonomic reflex arc. In simple terms the ANS consist of afferent path ways, central processing system and efferent pathways; ANS out flow is divided into two components. The throacolumbar sympathetic out flow and craniosacral parasympathetic out flow, whose effects are mostly antagonistic and whole balance activates to produce homeostasis in any systems. The peripheral out flow of the ANS are brought out by pregangliogenic and postganglonic nerves.

Autonomic innervations of cardio vascular system

The heart and vascular system are innervated by both parasympathetic and sympathetic nerves. The predominant supply of vagus is to the pace maker and conducting system and the sympathetic supply are more for cardiac muscle and vascular system. So the changes in the heart rate are predominantly modulated by the vagus and the contractility of cardiac muscle is brought by sympathetic pathway (Jalifc et al 19954).

Although some local factors, such as temperature, hormone changes and stretch of tissues can change the heart rate, the ANS is the principle way by which the heart rate can be controlled effectively.

We understand that the average resting HR is 70 beats/min in normal adults at rest and is very much greater in fetus and in children. During sleep the HR decreases around 10-20 beats/min and during emotional status and muscular exercise (any stress) the HR may go upto 2

times of the resting HR or more. The HR increase is due to the decrease in PNS and with increase in SNS. Though the two nerves act on SA node. The vagus in predominant in healthy and resting individuals. When healthy individual is given atropine, a muscarnic receptor antagonist that blocks parasympathetic (PNS) effects and so the heart rate increases sufficiently. If a healthy person is given propanolol, a β adrenergic receptor antagonist that blocks SNS, so the heart rate decreases only slightly. It is interesting to note that when both divisions of ANS is blocked the heart rate in young adults averages about 100 beats/min (Ganong. WF). The rate that prevails after complete ANS blockade is called the **intrinsic heart rate.** This is the most important concept that we have to understand. During the physiological stress however there is decreased parasympathetic activity and relative or absolute increase in sympathetic activity that causes changes in the CV function.

AUTORHYTHMICITY

The heart has its own inherent activity which is seen in spontaneously firing pacemaker cells in the wall of the right atrium. These cells are specialized cardiac muscle cells with scanty contractile fibers with large number of gap junctions. These cells have their membrane potential that after each impulse comes back to firing level what is called as **prepotential** (or) **pace maker potential**. At the peak of each impulse, potassium IK efflux begins and brings about repolarization. IK then delines, and has efflux decreases, the membrane begins to depolarize, forming the first part of prepotnetial, Ca2+ challnels then open. The calcium current (Ica) due to opening 'T' (Transchannels complete the prepontial followed by entry through L (Longlasting) channels to produce the impulse.

PARASYMPATHETIC PATHWAY

The cardiac parasympathetic fibers originate in the medulla oblongata cells that lie in the dorsal motor nucleus of the vagus (or) the nucleus ambiguous. In humans the vagal fibers pass through the neck close to the common carotid arteries and then through the mediastinum to synapse with the post ganglionic cells. The vagal post ganglionic pathways go across the right atrial epicardium to the SA node. These cells are located either on the epicardial surface within the wall of the heart. Most of the cardiac ganglion cells are located near the SA node and atrioventricular (AV) conduction tissue. The right vagus nerve affects predominantly SA node. Stimulations of this nerve slows SA nodal firing and can even stop it for several seconds. The left vagus nerve mainly inhibits AV conduction tissue to produce various degrees of AV blocks. But there is also overlapping, of left and right vagal fibres. Because of this overlapping, left vagal stimulation also depress the SA node, and right vagal stimulations impedes the AV conduction. Among right and left vagus, the right vagus predominately dominates the pacemaker cells of the heart in determining the heart rate changes.

SYMPATHETIC PATHWAYS

The cardiac sympathetic fibers originate in the intermediolateral horn cells (IML) of the upper six thoracic segments and lower two cervical segments of the spinal cord. The fibers emerge from the spinal column through white communicating branches and enter paravertebral chains of ganglia. The preganglionic and post ganglionic nerves synapse mainly in the stellate (or) middle cervical ganglia. In the mediastinum, the post ganglionic sympathetic fibers and preganglianic parasympathetic fibers join to form a complex plexus of the mixed efferent nerves to the heart.

The post ganglionic cardiac sympathetic fibers in this plexus approach the base of the heart along the adventitial surface of the great vessels (Schwartz PJ e al 1990). On entering the base of the heart, the fibers are distributed to the various chambers as an extensive epicardial plexus. They then penetrate the myocardium along the coronary vessels. The left side sympathetic fibers are distributed left side of heart having predominant role on the myocardial contractility. The right side sympathetic distribution carries the changes in the heart rate. There is also extensive crossing over of these fibers.

OVERALL INTEGRATION OF ANS

All the system in our body are well integrated. ANS is a perfect example of well integrated System. They receive and transmit information. Since there are so many variables associated with this system, it is not that much easy to study the complex integration. Since they are associated with vital function, it is necessary to describe those variables which are known to be related and to develop a methodology by which these variables may be examined, monitored and treated if necessary.

The control mechanisms of this reflexogenic system exist at various levels of neural axis. In the earlier studies supra segmental influence upon segmental level was done. At present, available literature provides information on the vital centers in pontomedullary mesencephalic reticular formation and also cerebral neocortical and paleocortical structures which integrate them. These regulator systems include simple reflexes in the brainstem and spinal cord as well as complex long circuit pathways through the higher brain centers. Higher centre of regulatory functions are located in the reticular formation of the brainstem and nuclei of the hypothalamus with a great influence from the limbic areas and the cerebellum. The very

fact that, every activity of the nervous system is associated with ANF and every activity of the cortex has a profound effect upon the autonomic regulatory controls. In the present study I have sincerely attempted to find out the CV ANF, in normotensive hypertensive subjects.

ROLE OF GENETICS IN HYPERTENSION

Introduction

Primary (or) essential HT is defined as a high blood pressure where no obvious secondary causes, such as renal disease, adrenal tumors, drug therapy (or) diabetics have been identified. Given a large number of environmental, behavioural, and genetics factors that can potentially influence blood pressure. Essential HT covers a wide range of underlying cause and although it would be extremely useful to subdivide primary HT for the purpose of treatment parameters. The genetic compliment of an individual may determine his / her ability to respond to such change to impinge on environmental factors.

Work by various investigators to isolate a “hypertensive gene” or “group of genes” have been going on for many years. Genetic effects of HT is polygenic in nature. This means that there are genetic loci which influence BP. Abnormalities in the angiotensin gene have been identified by (**Caulfield and co-workers**) provide evidence to link mutations in the angiotensin gene to the pathogenesis of essential hypertension. The possible genetic link between the presence of insulin resistance and the development of hypertension has been provided (Ferranmini et al 1987). Candidate genes are identified in number of ways. In some cases, a simple Mendelian form of HT can be identified by pedigree analysis. Detailed linkage analysis may then reveal the chromosome, the sub-chromosomal region, or even the gene most likely to be involved in HT, may be the result of small increments in the Blood pressure may be due to a number of contributing variants. Each of these may vary not only in phenotype but may also be affected by polymorphic allele frequencies, low peniterance and the epistatic effects of other genes.

Genome wide lineage analysis suggests that different sets of genes contribute to HT in different ethinic groups and the precise analysis is difficult in humans because of their heterogeneous genetic background. Recently developed micros-satellite database for human (Colin JR e al 2003), greatly aid whole genome scans. Any mutation that causes sustained salt retention concomitantly increase water retention and will raise blood pressure. The other way is also true causing hypotension (Physiological review 1986).

With rapid advances in functional genomics and proteomics that the majority of genes would be identified and mapped in the whole genome sequencing programs and subsequently will be classified and have functions assigned to them. Finally it is the interactions between gene products that mediate physiologic response. The delineation of a gene profile that will predict who will develop hypertension is very near. Data from the on going many studies may very soon, will lead to the identification of such genes within the next few years.

HEAR RATE VARIABILITY

Introduction

There has been no quantitative marker for – Cardiovascular Autonomic Function. Studies in the last 30 years has shown a great significance between ANS and CV morbidity, including sudden death and malignant arrhythmias (Levymn et al 1994). Heart rate variability represents the hallmark of such markers. At present may commercial devices provide automated measurement of HRV. Physiologist and clinical cardiology research scholars have made use of these instruments. But the precise measurement and meaning of HRV analysis being more complex. European society of cardiology and North American society of pacing and electrophysiology have contributed a Task force to develop appropriate standards. In this study I have followed the recommendations and guide lines of The Task force 1996 (Circulation 1996).

Back ground

The clinical use of HRV was well recognized when Hon and Lee in 1965 studied that, fetal distress was preceded by alterations in HRV before any notable change occurred in the heart rate itself. During 1970's (Ewing et al 1970) made simple bedside test of short term RR difference to detect a neuropathy in diabetic patients. In 1981 Akselrod et al (33) introduced first power spectral analysis of heart rate fluctuations to quantitative evaluation. The understanding of ANF on the basis of RR interval fluctuations in the heart rate is by two methods.

- Frequency domain methods
- Time domain methods.

Frequency domain methods

Though there are various spectral methods for studying RR tachogram, Power spectral density (PSD) analysis gives the fundamental information of how the power (Variance) distributes as a function of frequency (Rottamann et al 1990). By proper mathematical algorithms and estimate of true Power spectral density can be obtained. They are

1) Non-parametric method
2) Parametric method

The advantages of non parametric methods are

a) The simplicity of algorithm used fast fourier transform (FFT)
b) High processing speed

Spectral Components

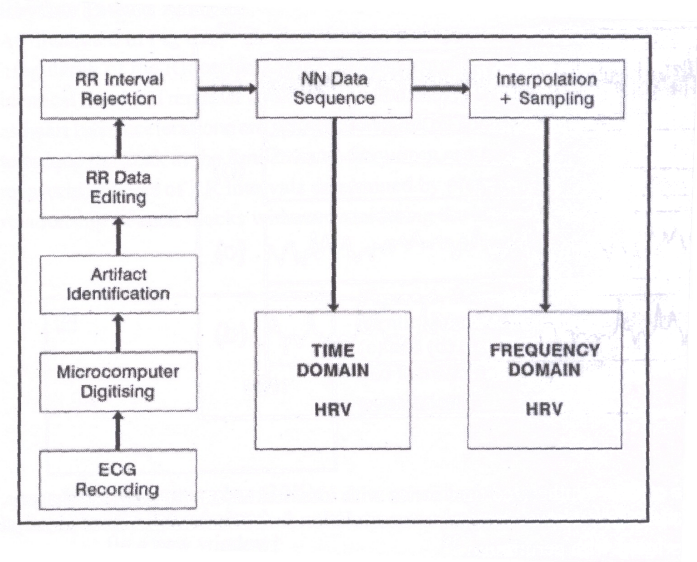
Short term recordings: In this study we have used only short time HRV that is for 5mins. The three main components are distinguished in a spectral calculation from short term ECG recording are (Akeslred S et al 1981) VLF, LF and HF

VLF - Very low frequency
LF - Low frequency
HF - High frequency

The distribution of power and central frequency of LF and HF are not fixed but may vary in relation to changes in autonomic modulations of the heart period (Paganim et al 1986). The physiological explanation for VLF component is much less defined and there changes brought about by changes in temperature and ACE inhibitors. The measurement of VLF, LF and HF power are usually made in absolute values of power (millisecond squared). Their frequency range is given as follows.

	Range (Hz)
VLF	**0.0 - 0.04**
LF	**0.04 - 0.15**
HF	**0.15 - 0.4**

Flow chart summarizing individual steps used when recording and processing the ECG signal in order to obtain data for HRV analysis.



LF and HF are also measured in normalized units(Mallinai A et al 1991), which represents the relative value of each power component in proportion to the total power mines the VLF component. So the representation of LF and HF in normalized units emphasis the controlled and balanced behaviour of the two branches of ANS. The usefulness of normalization, is to minimise the effect of changes in total power and the value of LF and HF components. In this study, we have quoted absolute value for LF and HF and also the normalized units for LF and HF. The ratio of LF and HF units give the autonomic modulation. If the modulations are constant, the interpretation of the results of frequency analysis is less well defined. In our physiological mechanism the heart period modulations are taking place every movement and so these changes are seen in LF and HF components. Thus spectral analysis are taken on the entire 24-hrs period as well as spectral results are obtained from shorter segments (5mints) averaged over entire 24hrs also (Furlan R et al 1990). It should be remembered that the components of HRV provide measurement of the degree of autonomic modulation rather than of the level of autonomic tone.

PHYSIOLOGICAL CORRELATIONS OF HRV

We know that the cardiac automaticity is intrinsic to pacemaker tissue; heart rate and rhythm being largely under the control of autonomic systems. The focus of this study is the oscillations in the interval between consecutive heart beats as well as oscillations between consecutive instantaneous heart rate. "**Heart rate variability (HRV)**" has become the conventionally accepted term to describe variations of both instantaneous heart rate and RR intervals. To describe oscillation in consecutive cardiac cycles, other terms have been used in the literature, for example, **cycle length variability, heart period variability, RR variability**,

and **RR interval tachogram**, and they are more appropriately emphasize the fact that it is the interval between consecutive beats that is being analyzed rather than the heart rate per se. however, these terms have not gained as wide acceptance as HRV; thus, I have used the term HRV in this document.

COMPONENTS OF HRV

RR interval at resting conditions represents a fine tuning of beat (Levy MN et al 1994) – to beat control mechanisms. Vagal afferent stimulations lead to reflex excitation of vagal efferent activity and inhibition of sympathetic efferent activity. The opposite reflex effects are mediated by sympathetic activity. Efferent vagal activity also appears to be under "Tonic" restraint by cardiac afferent sympatheties activity (Cerati D et al 1991). Efferent sympathetic and vagal activities directed to the sinus node are characterized by discharge, largely synchronous with each cardiac cycle that can be modulated by central (vasomotor and respiratory centers) and peripheral (oscillation in arterial pressure and respiratory movements) oscillators. These oscillators generate rhythmic fluctuations in efferent neural discharge that manifest as short-and long –term oscillation in the heart period. Analysis of these rhythms may permit inferences on the state and function of (a) the central oscillators, (b) the sympathetic and vagal efferent activity, (c) humoral factors, and (d) the sinus node.

An understanding of the modulatory effects of neural mechanisms on the sinus node has been enhanced by spectral analysis of HRV (Mallini A et al 1991). The efferent vagal activity is a major contributor to the HF component, as seen in clinical and experimental observations of autonomic maneuvers such as electrical vagal stimulation, muscarinic receptor blockade, and vagotomy. More controversial is the interpretation of sympathetic modulation (especially when

expressed in normalized units) and by others as a parameter that includes both sympathetic and vagal influence. This discrepancy is due to the fact that in some conditions associated with sympathetic excitation, a decrease in the absolute power of the LF component is observed. It is important to recall that during sympathetic activation the resulting tachycardia is usually accompanied by a marked reduction in total power, whereas the reverse occurs during vagal activation. When the spectral components are expressed in absolute units (milliseconds squared), the changes in total power, influence LF and HF in the same direction and prevent the appreciation of the fractional distribution of the energy. This explains why in supine subjects under controlled respiration, atropine reduced both LF and HF and why during exercise LF is markedly reduced. This concept is exemplified in showing the spectral analysis of HRV in a normal subject during control supine condition and 90^0 head-up tilt(Montano et al 1994). Because of the reduction in total power, LF appears as unchanged if considered in absolute units. However, after normalization an increase in LF becomes evident. Similar result apply to the LF/HF ratio also.

LF and HF can increase under different conditions. An increased LF (expressed in normalized units) is observed during 90^0 tilt, standing, mental stress, and moderate exercise in healthy subjects, and during moderate hypotension, physical activity, and occlusion of a coronary artery or common carotid arteries in conscious dogs. Conversely, an increase in HF is induced by controlled respiration, cold stimulation of the face, and rotational stimuli. To conclude HRV analysis has got wide application in clinical medicine such as diabetic neuropathy, Post Myocardial infarction (sudden death, malignant arrhythmias), autonomic function disturbances, myocardial dysfunctions, CVS drug therapy, vagal dominance identification, exercise training and many other clinical disorders.

AIM AND OBJECTIVES OF THE STUDY

1) To compare the cardiovascular autonomic function in male offsprings of (18 to 25 years) non-hypertensive and non-diabetic parents to the male offsprings of hypertensive, non-diabetic parents by

   i. BP and HR during supine rest to BP and HR response to standing, HRV during deep breathing and Valsalva ratio in Valsalva maneuver. HR and BP response during sustained isometric Hand Grip Test (SIHG) and during Cold Pressor Test (CPT).

2) To compare the usefulness of Heart Rate Variability Analysis to cardiovascular autonomic function test in either subjects.

MATERIALS AND METHODS

Subjects :

The subjects were undergraduate male students of Stanley Medical College Chennai. The students were briefed about the study procedure and a written and oral consent was obtained from them.

They were given a printed questionnaire (Appendix A) and based upon the written replies they were divided into two groups.

Group	Abbreviation used	No. of Subjects
Offsprings of Non Hypertensive, non diabetic parents. (Control)	ONHTP	25
Offsprings of Hypertensive, non diabetic parents (Study Group)	OHTP	25

INCLUSION CRITERIA

1) Healthy male individuals of 18 – 25 years.
2) Free from CVS and any other chronic illness.
3) Non smokers, non alcoholic, not on any drugs.

EXCLUSION CRITERIA

1) History of any neural or endocrine illness
2) History of autonomic dysfunction.

EXPERIMENTAL PROTOCOL

The tests were carried out in the neurophysiology of the Department of Physiology, Stanley Medical College, Chennai between 10.00 am and 1.00 pm. The laboratory environment was quiet, the temperature between 25 - 28 degrees Celsius and the lighting subdued. Subjects were asked to empty their bladder before the tests. The tests did not involve intravascular instrumentation or administration of any drugs at any stage.

EQUIPMENT

ECG was acquired using RMS Polyrite D hardware 2.2 (India), an instantaneous heart rate at RR intervals were continuously plotted using RMS 2.2 software on a Microsoft Window-based PC. The RMS polyrite software 2.2 helps to save multiple records and provided with additional filter settings, calculation tools, automated analysis and auto report generation. Respiratory movements were recorded using respiratory belt which analysis inspiration and expiration. Blood pressure was measured using the automated non-invasive BP monitor (Planet 50) L & T India. This measures BP by the oscillometric method. A standard adult – size cuff measuring 23 cm by 12 cm was used for all subjects.

METHODOLOGY OF CARDIOVASCULAR ANFT

The subjects were made to sit in the lab for 10min to get accustom to the new environment after emptying the urinary bladder. The subjects have been clearly instructed not to have Coffee, Tea or cool drinks 1½ hours before test. After through clinical examination (Appendix B) to rule out any acute or chronic illness also for any autonomic dysfunction, then their height in meters and weight in Kg measured. The students were then explained about the CV ANFT procedure. Then the battery of standard CV ANFT carried out which are as follows.

Procedure :

1) Electrodes were fixed in the following position after cleaning the site with sprit to record the ECG

Electrode	Position
Exploring electrode	Left shoulder
Exploring electrode	Right shoulder
Reference electrode	Right leg

2) Respiratory belt was tied around the chest at the level of nipple to record respiratory movement.

3) The electrodes and the respiratory belt were connected to RMS polyrite D equipment.

4) Blood Pressure cuff was tied to the right upper arm and connected to an automated non invasive BP monitor (Planet 50), L&T India.

i) Base line BP, HR & HRV :

ECG was recorded for 10mins to determined the HRV at supine rest with the eyes closed

with normal quite respiratory movement (12-16/min). Base line BP, was recorded at the end of 10mins at supine position.

ii) BP, HR & HRV response to standing :

After recording in the supine position the subjects were asked to stand without support on a wooden plank within 3 seconds and his BP and HR were recorded at the end of 5 sec, 2 mins and 5 mins after assumption of standing position.

iii) HRV During Deep Breathing

After recording the standing position the subject was asked to lie down comfortably in the supine position. He was then instructed to breath slowly and deeply at a rate of 6 breath per minute in such a way that he takes 5 seconds for each inspiration followed 5 seconds for expiration. The entire procedure was monitored on the screen

iv) Heart Rate Changes During Valsalva Maneuver.

I have made the subject to sit comfortably on a chair. I have instructed them to blow the air through the tube of the mercury manometer to keep the mercury pressure at 40mm and sustained at 40 mmHg for 15 sec. I have repeated this test 3 times with time interval of 3 minutes each. Valsalva ratio (VR) was obtained between the maximum RR and the minimum RR for each event and the maximum ratio was taken as the VR value.

V) BP and HR changes during Sustained Isometric Handgrip Test (SIHG)

Using hand dynamometer, I asked the subjects to produce 30% of maximum voluntary contraction on the non-dominant hand atleast for 60 sec. BP was recorded on the other hand at the end of 1 minute of sustained handgrip.

VI) BP and HR Changes During Cold Pressor Test (CPT).

The subject was seated comfortably and his left hand was immersed upto the wrist in the cold water 10±2 degrees Celsius for 1 minute. At the end of 1 minute BP was recorded on the other hand. Although the recommendation for CPT is $4^{O}C$ but our climatic condition allowed us to do at $10^{o}C$ for 1 minute.

TECHNIQUES OF HEART RATE VARIABILITY ANALYSIS :

A detailed account of techniques of heart rate variability analysis was mentioned in the Task force report of the European Society of Cardiology, 1996. Briefly, ECG was acquired at a rate of 1000 samples per second using RMS polyrite 2.2 software for atleast 330 seconds during supine at rest and then standing. The ECG was also recorded during deep breathing, isometric handgrip and cold pressor test. I checked the ECG for artifacts and ectopics. I have applied linear interpolation for NN intervals i.e. (Normal to Normal RR intervals). HRV analysis in frequency domain method was done by HRV analysis V 1.1 software.

FREQUENCY DOMAIN ANALYSIS

The artifact free RR interval tachogram (256 seconds) was resampled at 2 Hz and detrended, its mean removed and padded with zeros to obtain a 1024 point time-series. A Hanning window was applied to minimize special leakage and the series was analysed by linear fast Fourier transformation. A 512 point FFT spectrum with a frequency resolution of 3.9 mHz was obtained. The spectrum was further processed by applying a smoothing function (a smoothing factor of 7) to identify spectral densities contributing to cyclical behaviour of the series.

RR interval variations occurring in the frequency range 0-400mHz were chosen for analysis and a power spectrum obtained by squaring the magnitude of the Fast Fourier transform in this frequency range (Sands e al. 1989). Low frequency (LF) spectral power and high frequency (HF) spectral power of RR intervals were obtained by integrating the power spectrum from 40 mHz – 150 mHz and 150 – 400 mHz respectively (Sands et al, 1989). The LF/HF ratio was derived as the ratio of low frequency and high frequency spectral powers expressed in dimensionless units. Total power was calculated as the sum of the LF and HF powers. Power in the very low frequency range (VLF) (4-40 mHz) was not analysed since it is not reliably assessed in 5 minute recording (Sand et al., 1989). The LF and HF spectral powers in normalized units (nu) were calculated as shown below in the table.

Frequency – domain measures of HRV

Index	Units	Description
LF Power	ms^2	Power in the frequency band 0.04 – 0.15mHz
HF Power	ms^2	Power in the frequency band 0.15 – 0.4 Hz
Total Power	ms^2	Power in the band 0.04 – 0.4Hz
LF / HF ratio	-	Ratio of LF to HF powers
LF nu	-	LF power / (LF power + HF power)
HF nu	-	HF power / (LF power + HF power)

All these derivations comply with standards recommended by the Task force of the European Society of Cardiology and the North American Society for Pacing and Electrophysiology (1996).

ETHICAL CONSIDERATIONS :

The study was approved by Ethical Committee, Stanely Medical College, Chennai.

OBSERVATION

Table1
Anthropometry of subjects (Age, Weight & Height are expressed as mean ± SD)

	Group N = 25	N	Mean	SD	Independent t-test
Age	Control	25	19.72	1.90	t=1.82 P=0.07
	Study	25	20.84	2.41	
Height (Mts)	Control	25	1.6816	.051	t=1.71 P=0.09
	Study	25	1.7120	.072	
Weight (Kg)	Control	25	68.82	10.62	t=1.93 P=0.06
	Study	25	70.52	11.30	
BMI	Control	25	24.40	3.15	t=1.37 P=0.18
	Study	25	24.055	3.52	

Table 2
Resting Mean blood pressure and heart rate in supine position. Data are expressed as mean ± SD, 95% confidence interval of the mean.

	Group	N	Mean	Std. Deviation	Independent t-test
HR	Control	25	68.66	10.47	t=1.89 P=0.28
	Study	25	71.97	11.00	
SBP	Control	25	103.12	7.09	t=1.47 P=0.15
	Study	25	106.48	8.99	
DBP	Control	25	65.76	7.29	t=1.89 P=0.07
	Study	25	69.80	7.81	
PP	Control	25	37.20	7.76	t=0.67 P=0.51
	Study	25	38.72	8.28	
RPP	Control	25	7089.36	1228.35	t=1.58 P=0.12
	Study	25	7675.92	1397.72	

Table 3
Mean Heart rate and blood pressure response after 2 minutes of standing. Data are presented as mean ± SD, 95% confidence interval of the mean.

Parameters	Group n = 25	Rest	2 Minutes after standing	Paired t test
HR (bpm)	Control	68 ± 10	81 ± 10	t = 6.12 P = 0.001
	Study	71 ± 11	83 ± 11	t = 5.07 P = 0.001
SBP (mmHg)	Control	103 ± 7	112± 10	t = 4.22 P = 0.001
	Study	106 ±8	112± 9	t = 3.44

				P = 0.001
DBP (mmHg)	Control	65 ± 7	76± 8	t = 4.66 P = 0.001
	Study	69± 7	76± 6	t = 4.57 P = 0.001
RPP (mmHg bpm)	Control	7089 ± 1228	9243± 1717	t = 6.35 P = 0.001
	Study	7675 ± 1397	9468 ± 1745	t = 5.73 P = 0.001

Changes during standing were analyzed by Student's Paired 't' test.

Table 4

Mean Percentage Changes in heart rate and blood pressure during standing compared with baseline. Data are represented as mean ± SD, 95% confidence interval of the mean.

HR	Group	N	Mean (%)	Std. Deviation	Independent t-test
HR immed.	Control	25	36.57	19.26	t=3.18 P=0.03
	Study	25	19.65	18.28	
HR 2 min.	Control	25	20.53	17.25	t=0.49 P=0.62
	Study	25	18.02	18.40	
HR 5 min	Control	25	15.28	15.61	t=1.05 P=0.29
	Study	25	10.34	17.63	

SBP	Group	N	Mean (%)	Std. Deviation	Independent t-test
SBP immed.	Control	25	12.08	12.04	t=2.30 P=0.03
	Study	25	32	22.55	
SBP 2 min	Control	25	9.45	11.06	t=1.16 P=0.25
	Study	25	6.21	8.63	
SBP 5 min	Control	25	7.15	10.30	t=1.19 P=0.24

	Study	25	3.94	8.56	

DBP	Group	N	Mean (%)	Std. Deviation	Independent t-test
DBP immed.	Control	25	19.69	19.07	t=2.66
	Study	25	8.31	9.59	P=0.01
DBP 2 min	Control	25	17.90	19.27	t=1.63
	Study	25	10.62	11.29	P=0.11
DBP 5 min	Control	25	14.17	18.04	t=1.62
	Study	25	7.04	12.48	P=0.11

RPP	Group	N	Mean (%)	Std. Deviation	Independent t-test
RPP immed.	Control	25	53.32	28.98	t=3.71
	Study	25	21.11	32.30	P=0.001
RPP 2 min	Control	25	32.69	28.39	t=1.00
	Study	25	25.42	22.38	P=0.32
RPP 5 min	Control	25	23.92	23.88	t=1.42
	Study	25	14.83	21.20	P=0.16

Changes during standing were analyzed by Student's paired 't' test.

Table 5

Mean Heart Rate and blood pressure changes during sustained isometric handgrip. Data are presented as mean ± SD.

Group	Parameters	N	Mean	Std. Deviation	Paired t-test
Control	HR (Rest)	25	68.66	10.47	t=8.15
	HR (SIHG)	25	87.00	6.95	P=0.001
	SBP (Rest)	25	103.12	7.09	t=10.67
	SBP (SIHG)	25	123.08	11.07	P=0.001
	DBP (Rest)	25	65.76	7.29	t=13.82
	DBP (SIHG)	25	88.00	6.72	P=0.001
	RPP (Rest)	25	7089.36	1228.35	t=11.78
	RPP (SIHG)	25	10722.16	1381.18	P=0.001

Study	R_HR (Rest)	25	71.97	11.00	t=6.68
	HR (SIHG)	25	84.76	11.38	P=0.001
	SBP (Rest)	25	106.48	8.99	t=4.59
	SBP (SIHG)	25	118.52	12.86	P=0.001
	DBP (Rest)	25	69.80	7.81	t=4.33
	DBP (SIHG)	25	79.56	9.33	P=0.001
	RPP (Rest)	25	7675.92	1397.72	t=7.21
	RPP (SIHG)	25	10082.52	1902.40	P=0.001

Changes at rest and after the test were both compared with by Student's paired 't' test.

Table 6
Mean Heart Rate and blood pressure changes during Cold Pressor Test.

Group	Parameters	N	Mean	Std. Deviation	Paired t-test
Control	RHR (Rest)	25	68.66	10.47	t=8.62
	HR (CPT)	25	88.40	4.19	P=0.001
	SBP (Rest)	25	103.12	7.09	t=7.28
	SBP(CPT)	25	124.64	14.84	P=0.001
	DBP (Rest)	25	65.76	7.29	t=9.66
	DBP (CPT)	25	84.32	9.34	P=0.001
	RPP (Rest)	25	7089.36	1228.35	t=9.13
	RPP (CPT)	25	11040.40	1547.19	P=0.001
Study	R_HR (Rest)	25	71.97	11.00	t=7.26
	HR (CPT)	25	87.36	10.67	P=0.001
	SBP (Rest)	25	106.48	8.99	t=4.88
	SBP (CPT)	25	121.00	12.90	P=0.001
	DBP (Rest)	25	69.80	7.81	t=6.12
	DBP (CPT)	25	81.24	8.41	P=0.001
	RPP (Rest)	25	7675.92	1397.72	t=8.87
	RPP (CPT)	25	10585.08	1847.39	P=0.001

Changes at rest and after the test were both compared with by Student's paired 't' test.

Table 7

Control Deep Breathing for 1 minute

	Group	N	Mean	Std. Deviation	Student t-test
DB max/min RR Interval	Control	25	1.342	0.13	t=3.10 P=0.003
	Study	25	1.198	0.18	

Changes during controlled breathing were analyzed by Student's paired 't' test.

Table 8

Valsalva Ratio in Valsalva Maneuver

	Group	N	Mean	Std. Deviation	Student t-test
VR max / min RR Interval	Control	25	1.244	0.13	t=3.59 P=0.001
	Study	25	1.120	0.10	

Changes during valsalva maneuver were analyzed by Student's paired 't' test.

Table 9
30/15 ratio on immediate standing

	Group	N	Mean	Std. Deviation	Student t-test
30/15 sec RR Interval	Control	25	1.288	0.14	t=3.77 P=0.001
	Study	25	1.108	0.18	

Table 10
Heart rate and heart rate variability indices during supine rest. Data are expressed as mean ± SD, 95% confidence interval of the mean.

Parameters	Group	N	Mean	Std. Deviation	Student t-test
HR	Control	25	68.66	10.47	t=1.09
	Study	25	71.97	11.00	P=0.28
MEAN (RR) (ms)	Control	25	881.92	125.45	t=1.10
	Study	25	824.54	227.97	P=0.28
SDNN (ms)	Control	25	52.32	18.70	t=0.13
	Study	25	53.24	27.93	P=0.89
LF power (ms^2)	Control	25	363.44	235.30	t=1.14
	Study	25	587.32	947.50	P=0.26
HF power (ms^2)	Control	25	506.64	419.67	t=0.94
	Study	25	398.88	387.71	P=0.35
TOTAL power (ms^2)	Control	25	870.08	602.51	t=0.43
	Study	25	986.20	1225.69	P=0.67
LFnu	Control	25	32.14	33.49	t=1.04
	Study	25	44.79	15.44	P=0.30
HFnu	Control	25	55.197	15.44	t=2.31
	Study	25	44.42	17.41	P=0.03
LFHF ratio	Control	25	1.04	.98	t=1.99
	Study	25	1.69	1.32	P=0.05
NN50	Control	25	106.40	61.03	t=21.5
	Study	25	71.28	54.47	P=0.04

Table 11
Mann-Whitney Test
Test Statistics(a)

	nn50_hrv
Mann-Whitney U	291.500
Wilcoxon W	616.500
Z	-.408
Asymp. Sig. (2-tailed)	.683

a Grouping Variable: group

NN 50 and spectral powers of RR intervals during supine rest. Data are expressed as median, minimum – maximum.

	N	Mean	Std. Deviation	Minimum	Maximum
NN50	50	88.84	59.93	0	198
LF power (ms^2)	50	475.38	692.55	24	4246
HF power (ms^2)	50	452.76	403.55	37	1719
TOTAL (ms^2)	50	928.14	957.64	70	5216
GROUP	50	1.50	.50	1	2

	NN50	LF	HF	TOTAL
Mann-Whitney U	207.000	300.500	252.000	264.500
Z	-2.047	-.233	-1.174	-.931
Asymp. Sig. (2-tailed)	.041	.816	.240	.352

a Grouping Variable: group

Table 12

Heart rate and heart rate variability indices during standing. Data are expressed as mean ± SD, 95% confidence interval of the mean.

Parameters	Group	N	Mean	Std. Deviation	Student t-test
Mean HR (bpm)	Control	25	86.17	11.76	t=0.57 P=0.56
	Study	25	84.09	14.05	
Mean RR (ms)	Control	25	707.72	89.76	t=0.83 P=0.41
	Study	25	737.24	153.64	
SDNN (ms)	Control	25	43.40	16.55	t=1.04 P=0.31
	Study	25	48.36	17.30	
LF power (ms^2)	Control	25	435.12	349.62	t=0.52 P=0.61
	Study	25	491.52	413.55	
HF power (ms^2)	Control	25	194.60	240.35	t=0.16 P=0.87
	Study	25	184.96	170.09	
TOTAL power (ms^2)	Control	25	629.72	550.07	t=0.31 P=0.76
	Study	25	676.48	510.41	
LFnu	Control	25	72.73	12.75	t=0.13 P=0.89
	Study	25	73.22	12.70	
HFnu	Control	25	27.23	12.79	t=0.99 P=0.33
	Study	25	41.73	57.40	
LF/HF Ratio	Control	25	3.65	2.55	t=0.11 P=0.91
	Study	25	3.73	2.44	
NN50	Control	25	34.52	38.08	t=0.30 P=0.77
	Study	25	37.60	35.74	

HF special power and total special power did not follow a normal distribution.

Normality test-One-Sample Kolmogorov-Smirnov Test

		HF HRV	TOTAL Power
N		50	50
Normal Parameters(a,b)	Mean	189.78	653.10
	Std. Deviation	206.131	525.705
Most Extreme Differences	Absolute	.227	.163
	Positive	.227	.163
	Negative	-.188	-.129
Kolmogorov-Smirnov Z		1.603	1.149
Asymp. Sig. (2-tailed)		.012	.142

a Test distribution is Normal.

Descriptive Statistics

NN50 and spectral powers of RR intervals during standing. Data are expressed as median, minimum – maximum.

	N	Mean	Std. Deviation	Minimum	Maximum
LF power (ms^2)	50	463.32	380.071	44	1558
HF power ($ms^{2)}$	50	189.78	206.131	7	1052
TOTAL power (ms^2)	50	653.10	525.705	58	2209
NN50	50	36.06	36.587	0	164
Group	50	1.50	.505	1	2

Test Statistics(a)

	LF power (ms^2)	HF power (ms^2)	Total power (ms^2)	nn50_hrv
Mann-Whitney U	282.500	285.500	290.000	291.500
Wilcoxon W	607.500	610.500	615.000	616.500
Z	-.582	-.524	-.437	-.408
Asymp. Sig. (2-tailed)	.560	.600	.662	.683

NN 50 and spectral powers did not follow normal distribution. NN 50 and LF spectral power were analysed by Mann – Whitney Test.

Table 13
Summary of changes in heart rate and heart rate variability indices during standing. Data are expressed as mean ±SD.

Group	Parameters		Mean	N	Std. Deviation	Paired t-test
Control	Pair 1	Mean HR (Supine)	68.66	25	10.47	t=9.88
		MEAN HR (Standing)	86.17	25	11.76	P=0.001
	Pair 2	MEAN RR (Supine)	881.92	25	125.45	t=9.68
		Mean RR (Standing)	707.72	25	89.76	P=0.001
	Pair 3	SDNN (Supine)	52.32	25	18.70	t=2.84
		SDNN (Standing)	43.40	25	16.55	P=0.003
	Pair 4	LF power (ms^2) (Supine)	363.44	25	235.303	t=1.41
		LF power (ms^2) (Standing)	435.12	25	349.629	P=0.17
	Pair 5	HF power (ms^2) (Supine)	506.64	25	419.67	t=4.67
		HF power (ms^2) (Standing)	194.60	25	240.35	P=0.005
	Pair 6	TOTAL power (ms^2) (Supine)	870.08	25	602.516	t=3.05
		TOTAL power (ms^2) (Standing)	629.72	25	550.078	P=0.001
	Pair 7	LFnu (Supine)	32.79	25	15.44	t=8.29
		LFnu (Standing)	72.73	25	12.751	P=0.001
	Pair 8	HFnu (Supine)	55.19	25	15.44	t=8.30
		HFnu (standing)	27.23	25	12.791	P=0.001
	Pair 9	LF/HF (Supine)	1.04	25	.98	t=5.29
		LF/HF (Standing)	3.65	25	2.55	P=0.001
	Pair 10	NN50 (Supine)	106.40	25	61.033	t=6.56
		NN50 (Standing)	34.52	25	38.082	P=0.001
Study	Pair 1	Mean HR (Supine)	71.97	25	11.00	t=4.75
		Mean HR (Standing)	84.09	25	14.05	P=0.001
	Pair 2	Mean RR (ms) (supine)	824.54	25	227.977	t=1.92
		Mean RR (ms) (standing)	737.24	25	153.643	P=0.07
	Pair 3	SDNN (ms) (Supine)	53.24	25	27.93	t=1.14
		SDNN (ms) (Standing)	48.36	25	17.30	P=0.27
	Pair 4	LF power (ms^2) (Supine)	587.32	25	947.50	t=0.61
		LF power (ms^2) (Standing)	491.52	25	413.55	P=0.54
	Pair 5	HF power (ms^2) (Supine)	398.88	25	387.71	t=2.94
		HF power (ms^2) (Standing)	184.96	25	170.09	P=0.007
	Pair 6	TOTAL power (ms^2) (Supine)	986.20	25	1225.69	t=1.60
		TOTAL power (ms^2) (Standing)	676.48	25	510.41	P=0.12
	Pair 7	LFnu (Supine)	33.14	25	33.49	t=0.93
		LFnu (Standing)	76.22	25	12.70	P=0.36
	Pair 8	HFnu (Supine)	44.42	25	17.41	t=0.85
		HFnu (Standing)	41.73	25	57.40	P=0.40
	Pair 9	LF/HF Supine)	1.69	25	1.32	t=4.10
		LF/HF (Standing)	3.73	25	2.44	P=0.001
	Pair 10	NN50 (Supine)	71.28	25	54.47	t=3.89
		NN50 (Standing)	37.60	25	35.74	P=0.001

Changes during standing were analysed by Student's paired 't' test.

Table 14

Correlations between heart rate and frequency domain indices of heart rate variability. Data are expressed as spearman correlation coefficient rs, and P value respectively, 95% confidence intervals of Rs are mentioned when P values are ~ 0.05.

Group				Resting HR	LF Power	HF Power	TOTAL Power
Control	Spearman's rho	Restng HR	Correlation Coefficient	1.000	-.589(**)	-.588(**)	-.656(**)
			Sig. (2-tailed)	.	.002	.002	.000
			N	25	25	25	25
		LF Power	Correlation Coefficient	-.589(**)	1.000	.652(**)	.836(**)
			Sig. (2-tailed)	.002	.	.000	.000
			N	25	25	25	25
		HF Power	Correlation Coefficient	-.588(**)	.652(**)	1.000	.935(**)
			Sig. (2-tailed)	.002	.000	.	.000
			N	25	25	25	25
		TOTAL Power	Correlation Coefficient	-.656(**)	.836(**)	.935(**)	1.000
			Sig. (2-tailed)	.000	.000	.000	.
			N	25	25	25	25
Study	Spearman's rho	Resting HR	Correlation Coefficient	1.000	-.557(**)	-.646(**)	-.601(**)
			Sig. (2-tailed)	.	.004	.000	.001
			N	25	25	25	25
		LF Power	Correlation Coefficient	-.557(**)	1.000	.740(**)	.923(**)
			Sig. (2-tailed)	.004	.	.000	.000
			N	25	25	25	25
		HF Power	Correlation Coefficient	-.646(**)	.740(**)	1.000	.917(**)
			Sig. (2-tailed)	.000	.000	.	.000
			N	25	25	25	25
		TOTAL Power	Correlation Coefficient	-.601(**)	.923(**)	.917(**)	1.000
			Sig. (2-tailed)	.001	.000	.000	.
			N	25	25	25	25

Correlation was assessed by Spearman's correlation test. ** Correlation is significant at the 0.01 level (2-tailed).

Table 15

Correlation between resting systolic blood pressure and measures of overall resting heart rate variability. Data are expressed as Spearman correlation coefficient Rs and P value respectively. 95% confidence intervals of Rs are mentioned when P values are ~ 0.05.

Group				SBP_R	SDNN_R	TOTAL_P_R
Control	Spearman's rho	SBP	Correlation Coefficient	1.000	-.125	-.090
			Sig. (2-tailed)	.	.553	.668
			N	25	25	25
		SDNN	Correlation Coefficient	-.125	1.000	.860(**)
			Sig. (2-tailed)	.553	.	.000
			N	25	25	25
		TOTAL Power	Correlation Coefficient	-.090	.860(**)	1.000
			Sig. (2-tailed)	.668	.000	.
			N	25	25	25
Study	Spearman's rho	SBP	Correlation Coefficient	1.000	.072	.213
			Sig. (2-tailed)	.	.732	.307
			N	25	25	25
		SDNN	Correlation Coefficient	.072	1.000	.955(**)
			Sig. (2-tailed)	.732	.	.000
			N	25	25	25
		TOTAL Power	Correlation Coefficient	.213	.955(**)	1.000
			Sig. (2-tailed)	.307	.000	.
			N	25	25	25

Correlation was assessed by Spearman's rank correlation test.

** Correlation is significant at the 0.01 level (2-tailed).

Table 16

Correlation between resting Diastolic blood pressure and measures of overall resting heart rate variability. Data are expressed as Spearman correlation coefficient rs and P value respectively. 95% confidence intervals of Rs are mentioned when P values are ~ 0.05.

Group				DBP	SDNN	TOTAL_P_R
Control	Spearman's rho	DBP	Correlation Coefficient	1.000	-.067	-.045
			Sig. (2-tailed)	.	.750	.830
			N	25	25	25
		SDNN	Correlation Coefficient	-.067	1.000	.860(**)
			Sig. (2-tailed)	.750	.	.000
			N	25	25	25
		Total Power	Correlation Coefficient	-.045	.860(**)	1.000
			Sig. (2-tailed)	.830	.000	.
			N	25	25	25
Study	Spearman's rho	DBP	Correlation Coefficient	1.000	-.097	-.015
			Sig. (2-tailed)	.	.644	.945
			N	25	25	25
		SDNN	Correlation Coefficient	-.097	1.000	.955(**)
			Sig. (2-tailed)	.644	.	.000
			N	25	25	25
		Total Power	Correlation Coefficient	-.015	.955(**)	1.000
			Sig. (2-tailed)	.945	.000	.
			N	25	25	25

Correlation was assessed by Spearman's rank correlation test. ** Correlation is significant at the 0.01 level (2-tailed).

Table 17

Correlation between resting rate pressure product and measures of overall resting heart rate variability. Data are expressed as Spearman correlation coefficient rs and P value respectively. 95% confidence intervals of Rs are mentioned when P values are ~ 0.05.

Group				RPP	SDNN	TOTAL Power
Control	Spearman's rho	RPP	Correlation Coefficient	1.000	-.537(**)	-.556(**)
			Sig. (2-tailed)	.	.006	.004
			N	25	25	25
		SDNN	Correlation Coefficient	-.537(**)	1.000	.860(**)
			Sig. (2-tailed)	.006	.	.000
			N	25	25	25
		TOTAL Power	Correlation Coefficient	-.556(**)	.860(**)	1.000
			Sig. (2-tailed)	.004	.000	.
			N	25	25	25
Study	Spearman's rho	RPP	Correlation Coefficient	1.000	-.509(**)	-.423(*)
			Sig. (2-tailed)	.	.009	.035
			N	25	25	25
		SDNN	Correlation Coefficient	-.509(**)	1.000	.955(**)
			Sig. (2-tailed)	.009	.	.000
			N	25	25	25
		Total Power	Correlation Coefficient	-.423(*)	.955(**)	1.000
			Sig. (2-tailed)	.035	.000	.
			N	25	25	25

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Table 18

Correlation between resting systolic blood pressure and LF power, and systolic blood pressure and HF power. Data are expressed as Spearman correlation coefficient RS and P value respectively. 95% confidence intervals of RS are mentioned when P values are ~ 0.05.

Group				SBP	LF Power	HF Power
Control	Spearman's rho	SBP	Correlation Coefficient	1.000	.193	-.264
			Sig. (2-tailed)	.	.356	.202
			N	25	25	25
		LF Power	Correlation Coefficient	.193	1.000	.652(**)
			Sig. (2-tailed)	.356	.	.000
			N	25	25	25
		HF Power	Correlation Coefficient	-.264	.652(**)	1.000
			Sig. (2-tailed)	.202	.000	.
			N	25	25	25
Study	Spearman's rho	SBP	Correlation Coefficient	1.000	.257	.092
			Sig. (2-tailed)	.	.214	.663
			N	25	25	25
		LF Power	Correlation Coefficient	.257	1.000	.740(**)
			Sig. (2-tailed)	.214	.	.000
			N	25	25	25
		HF Power	Correlation Coefficient	.092	.740(**)	1.000
			Sig. (2-tailed)	.663	.000	.
			N	25	25	25

** Correlation is significant at the 0.01 level (2-tailed).

Table 19

Correlation between resting Diastolic blood pressure and LF power, and Diastolic blood pressure and HF power. Data are expressed as Spearman correlation coefficient rs and P value respectively. 95% confidence intervals of Rs are mentioned when P values are ~ 0.05.

Group				DBP	LF Power	HF Power
Control	Spearman's rho	DBP	Correlation Coefficient	1.000	.193	-.113
			Sig. (2-tailed)	.	.356	.590
			N	25	25	25
		LF Power	Correlation Coefficient	.193	1.000	.652(**)
			Sig. (2-tailed)	.356	.	.000
			N	25	25	25
		HF Power	Correlation Coefficient	-.113	.652(**)	1.000
			Sig. (2-tailed)	.590	.000	.
			N	25	25	25
Study	Spearman's rho	DBP	Correlation Coefficient	1.000	.017	-.073
			Sig. (2-tailed)	.	.936	.730
			N	25	25	25
		LF Power	Correlation Coefficient	.017	1.000	.740(**)
			Sig. (2-tailed)	.936	.	.000
			N	25	25	25
		HF Power	Correlation Coefficient	-.073	.740(**)	1.000
			Sig. (2-tailed)	.730	.000	.
			N	25	25	25

** Correlation is significant at the 0.01 level (2-tailed).

Table 20

Correlation between deep breathing difference and frequency domain indices of resting heart rate variability. Data are expressed as Spearman correlation coefficient rs and P value respectively. 95% confidence intervals of Rs are mentioned when P values are ~ 0.05.

Group				DB MAX/ MIN	LF Power	HF Power	TOTAL Power
Control	Spearman's rho	DB Max/Min	Correlation Coefficient	1.000	.399(*)	.108	.165
			Sig. (2-tailed)	.	.048	.608	.430
			N	25	25	25	25
		LF Power	Correlation Coefficient	.399(*)	1.000	.652(**)	.836(**)
			Sig. (2-tailed)	.048	.	.000	.000
			N	25	25	25	25
		HF Power	Correlation Coefficient	.108	.652(**)	1.000	.935(**)
			Sig. (2-tailed)	.608	.000	.	.000
			N	25	25	25	25
		Total Power	Correlation Coefficient	.165	.836(**)	.935(**)	1.000
			Sig. (2-tailed)	.430	.000	.000	.
			N	25	25	25	25
Study	Spearman's rho	D/B Max/Min	Correlation Coefficient	1.000	.112	-.158	.022
			Sig. (2-tailed)	.	.596	.451	.916
			N	25	25	25	25
		LF Power	Correlation Coefficient	.112	1.000	.740(**)	.923(**)
			Sig. (2-tailed)	.596	.	.000	.000
			N	25	25	25	25
		HF Power	Correlation Coefficient	-.158	.740(**)	1.000	.917(**)
			Sig. (2-tailed)	.451	.000	.	.000
			N	25	25	25	25
		Total Power	Correlation Coefficient	.022	.923(**	.917(**	1.000

					)	)	
			Sig. (2-tailed)	.916	.000	.000	.
			N	25	25	25	25

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Table 21

Correlation between resting Rate pressure product and LF power, and Rate Pressure Product and HF power. Data are expressed as Spearman correlation coefficient rs and P value respectively. 95% confidence intervals of Rs are mentioned when P values are ~ 0.05.

Group				RPP	LF Power	HF Power
Control	Spearman's rho	RPP	Correlation Coefficient	1.000	-.385	-.617(**)
			Sig. (2-tailed)	.	.058	.001
			N	25	25	25
		LF Power	Correlation Coefficient	-.385	1.000	.652(**)
			Sig. (2-tailed)	.058	.	.000
			N	25	25	25
		HF Power	Correlation Coefficient	-.617(**)	.652(**)	1.000
			Sig. (2-tailed)	.001	.000	.
			N	25	25	25
Study	Spearman's rho	RPP	Correlation Coefficient	1.000	-.347	-.519(**)
			Sig. (2-tailed)	.	.089	.008
			N	25	25	25
		LF Power	Correlation Coefficient	-.347	1.000	.740(**)
			Sig. (2-tailed)	.089	.	.000
			N	25	25	25
		HF Power	Correlation Coefficient	-.519(**)	.740(**)	1.000
			Sig. (2-tailed)	.008	.000	.
			N	25	25	25

** Correlation is significant at the 0.01 level (2-tailed).

RESULTS

A list of tables are mentioned in pages 30 to 48. The anthropometric characteristics of subjects are given in table – 1. Baseline blood pressure and heart rate are mentioned instable 2. The results of cardiovascular functions test are presented in table 3 to 9. To find out the difference between the groups. I have made use of paired 't' test. Results of HRV and other correlations are done using spearman's rank correlation test.

Results of heart rate variability analysis are presented in tables from 10 - 13. Results of correlation between resting HR, BP, deep breathing (db) and HRV indices are presented in tables 14 to 21. All reported P values are two – tailed.

My primary aim has been to compare autonomic functions in off springs of hypertensive parents. I have used unpaired students 't' test excepting where the compared variances were inhomogeneous. In that case I have used the Mann Whitney test.

1) Anthropometric Measurements Table - 1

There was no difference between the control and study group with regards to age, height, weight and BMI ($P > 0.05$).

2) Resting BP and HR in supine position Table -2

There was no significant difference between the control and study group with regards to HR, BP, PP, RPP ($P > 0.05$).

3) HR and BP response on 2 minutes on standing Table – 3

Both control and study group showed a very highly significant increase in HR, BP, RPP during standing ($p < 0.001$).

4) Percentage changes in HR, BP during standing compared to base line Table -4.

a) There was a significant increase in HR and SBP in study group immediately on standing ($p < 0.05$).

b) There was highly significant increase in DBP of study group immediately on standing. ($p < 0.01$).

c) The percentage increase in HR, SBP, DBP and RPP of both the control and study group were not significant ($p < 0.05$). Although there was a greater increase of the above variables in the control group compared to the study group.

d) Percentage increase in RPP in the study group was very highly significant immediately on Standing ($p < 0.01$).

5) HR & BP changes during SIHG Table – 5

The HR, SBP, DBP and RPP showed a very highly significant increase in the control group compared to the study group during SIHG. ($p < 0.001$). Although the resting HR, SBP, DBP, RPP were higher in the study group.

6) HR and BP changes in CPT Table – 6

The HR, SBP, DBP and RPP showed very highly significant increase in the control group compared the study group during CPT ($p<0.001$). Although the resting HR, SBP, DBP and RPP were higher in the study group.

7) Controlled Deep Breathing for 1 minute Table -7

The mean ratio of maximum / minimum in RR interval during 1 minute of controlled deep breathing was highly significant decrease in the study group compared to the control group ($p < 0.003$).

8) Valsalva Ratio in Valsalva Maneuver Table – 8.

The mean ratio of maximum / minimum in RR interval during valsalva maneuver was very highly significant decrease in the study group compared to the control group ($p<0.001$).

9) 30/15 ratio on immediate standing Table – 9

This showed are decrease in the study group compared to the control group which was very highly significant ($p < 0.001$).

10) Mean Resting HR and HRV in supine rest Table – 10.

a) HR / minute in the study group shown increased compared the control group which was statistically insignificant ($p< 0.05$).

b) The mean RR interval of the study group were lesser than the control group ($p < 0.05$).

c) SDNN (ms) shown that there was no significant change in between the study group and control group.

d) LF ms^2 in the study group showed an increase on standing when compare to the control group.

e) HF power . The HF power showed a decrease in the study group when compare to the control group. ($p < 0.05$)

f) Total power showed an increase in the study group was statistically insignificant.($p < 0.05$).

g) LF (nu) the study group showed a highly significant change ($P< 0.001$).

h) HF (nu) there was a significant decrease in HFnu in the study group compared to the control group.

i) LF/ HF ratio showed a significant increase in the study group compared to the control group.

j) NN50 showed a decrease in the study group compared to the control group.

Two groups were matched for age and BMI. Between the two groups, difference in baseline SBP, DBP, PP and RPP were statistically not significant, But certainly the resting HR, SBP, DBP and RPP were higher in study group compared to the control group.

The base line DBP (P=0.07). This may be an expression of early vascular changes in subjects with a genetic predisposition to hypertension (Saguaro et al 1995). The difference in the heart rate at the end of 5 mts of supine rest were not (P=0.28) significant.

HR and BP response to standing

The HR and BP response to standing in two groups have been assessed by comparing baseline HR, BP with HR and BP after 2 minutes of standing (table3). After two minutes of standing all the two groups showed a statistically significant increase in the (P=0.001). In all the groups, the percentage

increment in HR was greatest immediately after standing, whereas the percentage increment in SBP and DBP were maximum immediately after standing (table 4). To distinguish different in BP and HR reactivity to standing, percentage changes in BP, HR and RPP from baseline were analyzed immediately, after 2 minutes and after 5minutes of standing. Percentage changes were analyzed since there were significant differences in baseline BP. The control group showed a greater percentage increase (20.53+17.2) in HR after 2 minutes. After 5 minutes of standing the control group still showed the greatest percentage increase in HR (15.28 + 15.6) with respect to baseline when compared to study group. However, this difference was not statistically significant.

Deep breathing:

A controlled deep breathing for one minute between the control (1.342 + 0.13), study group (1.198+0.18) (Table 7) Normal values by age for deep breathing difference (db ration) at 16 to.25 years age is 1.21 (smith et al 1995). In the control group there was increase in the db ration and in study group there was reduction in db ration. There was a significant db ratio reduction in the study compared to control group (P=0.003). .

HR and BP response to sustained isometric handgrip:

All two groups showed statistically significant (P=0.001) in HR, SBP, DBP and RPP during sustained isometric hand grip (table 5). In both groups RPP remained higher compared to baseline (P=0.001). The resting RPP in control group in lower (7089 + 1228) compared to the resting RPP in study group (7675 + 1397).

HR and BP response to cold pressor test

The result of CPT is given in table 6. Both groups showed a statically significant change in the RPP. However the resting HR, SBP and DBP higher in the study group compared to the control group. There was no significant change in RPP at the end of CPT.

VALSALVA RADIO IN VALSALVA MANEUVER

The valsalva ration during (VR) valsalva maneuver of the two groups given in table 8. The VR

for control is 1.244 + 0.13 and the study group is 1.120 + 0.10. The ratio of 1.2 or greater is thought to be normal (Ewings et al 1997) . The control group is higher than the study group compared to the standard values. There was a statistically significant (P 0.001) VR compared in between two groups.

30:15 RATIO ON IMMEDIATE STANDING.

The cardio vascular response to standing is assessed by 30:15 ratio. The 30:15 ratio of control group (1.288 + 0.14), the study group (1.108 + 0.18) (table9). The age related value is 1.07 (Ewings et al 1974). Here both the group show above the normal value but when compared in between the two groups there in statistically significant 30 : 15 ratio (P=0.001) reduction in the study group compared to the control group.

RESULTS OF HEART RATE VARIABILITY.

RESTING HEART RATE VARIABILITY

The mean RR of two groups during 5 minutes of supine rest was comparable (Table 10). Although difference in SDNN between two groups were not significant (P=0.89). Since NN50 Value did not follow the normal distribution, they were analyzed by Mann – Whitney test.

The LF powers at rest in the control group 363 + 235 m^2 the study group 587 + 947 m^2 respectively. The standard deviation is higher because the range is very vide.

The HF power (m^2) of control group is 506 + 419 and the HF Power (m^2) of study group is 398 + 387. This shows there was a reduction in HF power in the study group which is again analyzed by Man- Whitney test. The total power of control and study of mp are 870 + 602, 986 + 1225 respectively. When LF powers and HF Powers were normalized, the differences between two groups were not statistically significant.

HEART RATE VARIABILITY DURING STANDING

The mean heart rate and heart rate variability of the two groups during standing are given in table 12. The differences in mean RR during standing were not significant. NN 50 and LF power did not follow a normal distribution and have been analyzed by one sample kolmogorov-smirou test. The

difference in NN50 between control and study group appears to be clinically important. NN50 and LF power did not follow a normal distribution and so they are analyzed by Kolmogorou-smirou test. Also, the LF power is higher 491+ 413 in the study group compared to control 435 + 349. The total power is also increased in study group 676 + 510 compared to control 629 + 550.

In all two groups resting HR and HRV indices have been compared with HR and HRV indices during standing (p = 0.001) also statistically significant total power, HF power, LF nu, HF nu LF / HF ratio and NN50.

RESULTS OF CORRELATION BETWEEN RESTING HR, BP, BREATHING DIFFERENCE AND HRV INDICES.

The correlation between HR, BP, deep breathing and HRV indices were tested by spearman's rank correlation test. The results are shown in (Table 14-21).

CORRELATION BETWEEN RESTING HR AND FREQUENCY DOMAN HRV INDICES

In the control group the negative correlation (p=0.002) between LF power and HR was significant, also the negative correlation between HF and total power were significant (p = 0.002). In the study group the negative correlation between LF power and HR was significant (p = 0.004),also there was a negative correlation between HF and total power which were significant (p = 0.001).

CORRELATION BETWEEN SBP, DBP, RPP AND HRV INDICES

(Table 15, 16) Broth control and study group show negative correlations between SBP and measures of overall HRV were insignificant. In the control group, the negative correlation between DBP and SDNN was insignificant. In the control group there was a negative correlation between RPP and total power which was significant (p = 0.004). In the control group the negative correlation between RPP and total power which were not significant.

DISCUSSION

The autonomic nervous system and the balance between PNS and SNS output play an important role in overall cardiovascular homeostais. The fact that HRV responses are significantly lower in study group in consistent with the prevalence of a hyperdynamic circulatory state during maneuvers such as orthostatic load, isometric hand grip, CPT etc. This fact has been previously noted by (Julius et al 1990).

There was no clear evidence of a significant difference in overall heart rate variability as measured by SDNN. Also there was very little difference in the power in respiratory sinus arrhythmia, quantified by deep breathing and HF power at rest. However there was significant increase in the low frequency modulation of heart rate at rest in study group, this was measured in terms of absolute units of power. The LF in nu in the study group at rest was greater compared to control group (Stolorzk et al 2003). Although SDNN, the square root of variance, is a reliable measure of overall HRV, it does not provide any information as to how fast the heart rate response could be mediated. The other important and interesting difference between control and study group was the significant higher LF/HF ratio in study group even in supine position. This is due the greater LF modulation and lesser HF modulation of HR in the study group. So it was evident that LF modulation was most likely due to the sympathetic overactivity (Taylor et al 1996). This in turn occurs due to centrally originating oscillations in sympathetic drive to the blood vessels. This indirectly implicating that the group may become overtly hypertensive early in their life (ES Prakash et al 2004). LF / HF ratio in the supine position during normal quit breathing at 12 to 16/min is not a good indicator for sympathovagal interplay as the LF component which is a measure of sympathetic activity is very little during supine position and most of HRV in supine position is due to vagal modulation which could be abolished by atropine (Pagami et al 1986). But the ratio assumes significance on standing since there is either a vagal withdral or an increase or sympathetic activity on standing in the study group where the LF/HF ratio has

significantly increased.

RESTING BP, HR AND SUPINE POSITION

The resting HR and BP were higher in the study group. Although they were statistically insignificant, an increase in the diastolic pressure may be an expression of early vascular changes in the subjects with a genetic predisposition to hypertention. (Sagura et al 1995).

HR, BP , RPP response to standing

The HR, BP, RPP showed a very significant increase in both the study and control group during standing. The percentage increase in the HR, BP, SBP, RPP immediately on standing were significantly lower in the study group. Although the percentage change in the HR, BP, RPP after 2 minutes and 5 minutes of standing shown an increase in both group. It was statistically insignificant. The autonomic responses triggered to buffer the effects of gravity on the circulation produced by standing are complex, relying mainly on functional specialized stretch receptors (baroreceptors) that activate baroreflexes and the effects of local venoarteriolar axon reflexes. The exercise reflex (Coote et al 1971), capillary fluid shift systems, and the effects of endothelial and neurohormonal factors that modulate baroreflexes or act directly on blood vessels and the heart and kidneys play additional roles in the response to standing peripheral vascular resistance increase through sympathetic vasoconstriction and heart rate increases due to both vagal withdrawal and sympathetic activation. The net effect is an increase in heart rate and an increase in blood pressure to maintain values close to those while supine (although the pulse pressure may be diminished) (Rowell 1993). Simple procedures such as the measurement of upright blood pressure and heart rate provide important information regarding the integrity of the reflex mechanism that are triggered to compensate for the effects of gravity on the circulation.

30/15 Ratio on immediate standing

Studying the heart rate during the initial 30 sec after active standing provides an estimate of cardiac parasympathetic control as the changes in heart rate are largely mediated by parasympathetic withdrawal and activation reflecting the changes in baroreceptor afferent traffic. Continuous heart rate

recording during the immediate response to standing have demonstrated heart rate peak at 3 and 13 sec followed by a slowing at 20 sec. The first heart rate peak is at about 3 sec due to withdrawl of vagal tone. This is followed by a gradual increase heart rate and a second peak that reaches a maximum at about a 12 sec due to both withdrawal of vagal tone and increased sympathetic tone. Within seconds of this initial response, venous return raises due to the pumping effects of limb and abdominal muscle contraction during the effort of standing and blood pressure over suits transiently. This raise in blood pressure is detected by barorecptors (barorecptors are loaded). Leading to reflex parasympathetic activation with slowing of heart rate which reaches a nadir at about 20 seconds (about 30th heart beat) after active standing. The heart rate variation during is almost completely abolished by atropine, but unaffected propranolol, indicating that this it is under vagal control (Ewing et al 1980). A reproducible ratio calculated from the maximum and minimum RR intervals at about 15 and 30th beats after standing is frequently used to measure vagal function. Normally, the ratio is greater than 1.04. In my study although both the groups showed a ratio more than 1.04, the study group had a value which was highly significantly lower, which could be due to early parasympathetic attenuation.

BP AND HR CHANGES DURING SUSTAINED ISOMETRIC AND GRIP TEST

Sustained isometric hand grip against resistance causes an increase the HR and arterial blood pressure. The cardiovascular response are mediated partly by central command and partly by metabolic or mechanical changes, or both, in contracting muscle that activate small fibres in the afferent limb of the reflex arc. Sustained muscle contraction causes increased BP and HR as a result of exercise reflex which withdraws parasympathetic and increases sympathetic activity. The BP changes are regulated by sympathetic adrenergic vascular function and the heart rate changes by parasympathetic cholinergic (Cardiovagal) function. This is well documented in our study where there is increase in HR, BP and RPP in the control group whereas the study group did not show a significant increase in above parameters.

BP AND HR CHANGES DURING COLD PRESSOR TEST

The normal response to immersion of a hand in ice water involves reflex arterial vasoconstriction producing increase in blood pressure and cardiac output by cutaneous pain receptors. Blood pressure is raised mainly through increased vascular resistance due to enhanced sympathetic activity. The initial increase in heart rate is blunted by β - adrenoreceptor blockers suggesting that sympathetic rather than parasympathetic outflow mediates this response. While the cold pressor test has been used to assess the efferent sympathetic outflow, the response involves a reflex arc that inclues afferent sensory nerve (pain), spinothalamic tracts, suprapontine and intrathalamic relays in addition to efferent sympathetic pathways, peripheral sympathetic receptors. Our study confirms the earlier works that there was a decrease in RPP in the study group which possibly due to reduced HRV immediately following the maneuver (ES Prakash et al 2004).

OVERALL HEART RATE VARIABILITY :

The differences in SDNN were not statistically significant. The overall SDNN in both the groups were more than 50 milliseconds at supine rest. The SDNN computed for 24 hours is a good predictor for mortality after myocardial infarction (ATRAMI Study 1998).

FREQUENCY DOMIN INDICES OF HRV

The short term (5minutes) ECG recording (Task force 1996) gives the mechanisms influencing heart period modulation. HRV occurring in the frequency range 40-400 MHz is mainly due to two important mechanisms – tonic vagal activity and reflex vagal activity. It is necessary to appreciate and understand that power with in this range (40-400 MHz) signifies the extent to which HR is modulated by acetylcholine released upon stimulation of instantaneous heart rates and it is also quite dependent upon the sensitivity of effectors to acetylcholine. It does not imply and also do not correlate with vagal traffic. So vagal tone is better quantified by change in heart rate induced by atropine following total beta blockade (Steinpk et al 2005). But in our study we found the total power is increased in the study group both in supine and standing position. If NN 50 in the measure of vagal activity it is very clearly and significantly increased in the control group compared to the study group in supine position. This

indicates that there is early vagal attenuation occurs in the study group at this age itself. (Task force 1996) report.

CORRELATION BETWEEN BLOOD PRESSURE AND HRV INDICES

Both SBP and DBP were higher in the study group even at supine rest (Marer JR et al 2004) and there was a negative correlation between SDNN and DBP in both the groups. The resting RPP was higher in the study group. The negative correlation between RPP and total power suggests that the common denominator between the two is the activation of the sympathetic nervous system. RPP is taken RPP as a simple index of myocardial oxygen consumption, the sympathetic effect on the CV system, then its negative correlation with HRV indices was quite understandable. Significant correlation between heart rate, RPP, deep breathing, and frequency domain indices of HRV support the easy approach in the evaluation of autonomic function.

HEART RATE VARIABILITY DURING DEEP BREATHING

The normal value for deep breathing for age group 18 – 25 years was 1.21 (Smith et al 1995). In our study the control group showed a deep breathing of 1.34. The slight increase was due to ethnic variation. A significant decrease of DB in the study group is a sensitive, specific and reproducible measure of cardiac vagal function, which acts centrally as well as peripherally. The decrease in the DB in the study group may be due to reduced baroreflex sensitivity or impaired vagal afference to the brain or an impaired ability of the brain stem to recognize the different signals resulting in an altered efferent signal to the heart a produce decreased cardiac parasympathetic activity (Hirsch JA et al 1981).

Measuring heart rate variability during 1 minute of controlled deep breathing (6 cycles 1 mt) is a sensitive, specific and reproducible measure of cardiac vagal function. The db in the control was 1.34 + 0.13 and in study group it was 1.19 + 0.18. There was a very high significant ($P<0.001$) reduction in the study group. The basis of this finding was mainly vagus which has got multiple levels of nuroaxis including peripheral and central mechanisms.

The PNS to heart may be decreased, may be due to reduced Baroreflex sensitivity, impaired vagal afferents to the brain, and impaired ability of the brainstem to properly recognize the different signal and hence altered efferent signals to the heart to decrease cardiac parasympathetic actively. The findings of this study correlate (Hirsch. JA et al 1981).

HEART RATE RESPONSE TO VALSALVA MANEUVER

During valsalva maneuver there are changes in cardiac vagal efferent and sympathetic vasomotor activity, resulting from stimulations of carotid sinus and aortic arch baroreceptors and other intrathoric stretch receptors. The valsalva ratio is the measure of both parasympathetic and sympathetic function. In my study the valsalva ration (VR) for control group (1.24 + 0.13) and study group was (1.12 +0.10). There is statistically significant reduction in the study group. The VR of 1.2 or more in thought to be normal (Ewings et al 1977). Then the study group is well below the value of 1.2.

The factors in combinations may tend to decrease left ventricular output during the strain of the valsalva maneuver and decreased evoked tachycardia and vasoconstriction. So falling VR in the study group is the early physiological adaptation of chromic volume overloads state.

It is indeed necessary to control the BP at an optimum limits. Over many years adequate control of BP meant a clinic reading <140/90 mmHg obtained in the sitting position. But it is necessary to assess cardiovascular reactivity to such laboratory stressors in as much as these mimic the activity of daily life like standing, sustained isometric handgrip, cold pressor test, mental arithmetic are simple, laboratory physiologic equivalents of activities of daily life and it may be more useful to assess BP responses to such activity rather than assess the resting blood pressure alone (ES Prakash et al 2004).

The reasons for employing battery of autonomic function test takes time to perform and often require sophisticated and expensive equipment and software for data acquisition and analysis. The interpretation is often difficult since the underlying physiological mechanism are not really understood. In view of the complex nature of the hypertensive phenotype, it is very difficult to make generalization about the predictions of further hypertensive. Since it appears that the genesis of most primary

hypertension has its base in the central nervous system, it is worth to examine autonomic profile in the offsprings of Hypertensive parents who my develop hypertension in near future.

Ewings test – use fullness in assessing CV autonomic function in normotensive hypertensive subjects

These test are useful in evaluating CV autonomic function in normotensive hypertensive subjects. The pressor responses are mediated by the sympathetic nervous system and heart rate responses are for most part, vagally mediated (Stephen et al 2002)..

HOW FOR HRV ANALYSIS IS USEFUL IN THE EVALUATION OF OUR SUBJECTS.

Autonomic function evaluations with HRV analysis is not without problems. The indices obtained are very complex and any valued interpretation needs a clear knowledge of mechanisms of cardiovascular regulation. Many times I come across an open – ended questions and interpreting HRV analysis is not an easy task. Single measurements is even more difficult to interpret since there are wide variation in most of the HRV indices. HRV analysis requires well advanced data acquisition systems and expensive software and persons trained to analyze and interpret the result. The autonomic state that exists in a normotensive is influenced by a number of factors including physical activity, duration of changes and presence of other risk factors of cardiovascular systems.

CONCLUSION

Cardiovascular autonomic function in normotensive hypertensive subjects have shown

- Significant increase in LF power in HRV
- Very slight decrease in overall heart rate variability in study group
- The increase of LF modulation and RR interval as a decrease in overall HRV (an indicator of decreased baroreflex sensitivity) may be due to centrally originating sympathetically mediated BP oscillation. This may be an early prediction of normotensive hypertension concept.
- The cardiovascular autonomic function and HRV analysis provided an additional information about the normotensive hypertensive concept.
- The following are very significantly decreased in the study group,
    - 30/15 ratio on immediate standing
    - Deep breathing (maximum / minimum RR interval)
    - VR ratio in valsalva meneuver
- Further study along these lines could give more information in understanding cardiovascular autonomic function in clinical settings.

SUMMARY

This study was aimed to compare the CV autonomic function in subjects with offsprings of hypertensive to offsprings of nonhypertensive nondiabetic parents. The subjects were divided into two groups of 25 males of age group 18-25 years.

Control group – offsprings of nonhypertensive nondiabetic parents

Study group – Offsprings of hypertensive nondiabetic parents.

The following tests were performed:

- Blood Pressure and HR Response at supine rest
- Blood Pressure and HR Response during quite standing.
- Controlled deep breathing 1 minute
- Valsalva ratio in valsalva maneuver
- Sustained isometric hand grip test.
- Cold pressor test.

The following results were obtained :

- 30 : 15 ratio on standing(very high significant reduction in study group)
- Deep breathing for 1 minute max RR / minim RR (significant reduction in study group)
- Valsalva ratio (VR)(very high significant reduction in study group)
- RPP was more at the rest in the study group, but no significant changes during SIHG and CPT.

The following results were obtained in HRV analysis:

- The mean RR is increased in the study group
- SDNN there is no very much difference
- LF power increased in the study group
- HF decreased in the study group.

- Total power increased in the study group
- LFnu increased in study group on standing
- HFnu decreased in study group on standing

All these observations indicate very early small reduction in vagal modulation of RR intervals in the study group. An increase in LF Power in the study group gives an idea of sympathetic over activity. But there is no clear evidence of increased sympathetic activity at this stage.

So bedside assessment of measuring blood pressure alone may not reflect the actual physiology in the prediction of normotensive hypertensive concept. But on the other hand the autonomic function test and HRV analysis could also give more information in understanding the regulation of blood pressure.

APPENDIX B

CLINICAL SYMPTOMS / HISTORY PROFORMA

Autonomic Function Laboratory

Department of Physiology SMC, Chennai.

Name _____ Age/Sex_____

I.D. ..... Date _____

No.	Autonomic Symptoms		Yes	No
1.	Nasal symptoms:	a. dry nose		
		b. running nose		
2.	Sweating disturbances:	a. increased		
		b. decreased		
3.	Postural fall/dizziness on standing:			
4.	GIT symptoms:	a. Diarrhoea		
		b. Constipation		
		c. Discomfort/Pain		
		d. Stool frequency (per day)		
5.	Headache/Migraine (Heaviness of head/throbbing headache):			
6.	Micturition disturbances:	a. Frequency		
		b. Urgency		
		c. Incontinence		
		d. Nocturia		
		e. Hesitancy		
7.	Occasional attack of bronchospasm (after exercise, laughter or emotion, not diagnosed as Bronchial Asthma):			
8.	Do you often feel too hot/too cold:			
9.	Do your extremities remain:	a. warm		
		b. cold		
10.	Burning feet:			

11.	Risk Factors:			Self	
		Yes	No	Yes	No
	Alcoholism				
	Diabetes Mellitus				
	Hypertension				
	Heart attack (CHD)				
	Obesity				
	Smoking				

12.	Any stress related physical symptoms: (Flushing, choking, lump in the throat, general weakness, tremors)					
13.	Any other general symptoms:					
14.	Allergy to any drug:					
15.	Physical status:	Regular athlete	Occasional player	Regular exercise	sedentary	

APPENDIX A

PROFOMA : PARENT DATA COLLECTION

Department of Physiology SMC Chennai

NAME OF THE STUDENT:

AGE OF THE STUDENT :

ROLL NO. :

YEAR OF COURSE :

DATA OF THE PARENT :

NAME	AGE (yrs)	BP (mm/Hg)	TREATMENT YES/NO	SPECIFY THE DRUGS	DIABETIC YES/NO

ADDRESS OF THE PARENT :

DATE : **SIGNATUE OF THE STUDENT**

MOBILE NO :

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APPENDIX D

Consent Form

I Mr. _____Understand that **Dr. xxxxxxx**, a postgraduate student in Stanley Medical College and Hospital, Chennai is doing this study on subjects with Normotensive Hypertensive. I am given to understand that these tests will assess the functioning of my heart and blood vessels. These tests are simple; involve taking ECGs, blood pressure and respiratory movements. They do not involve injections or taking any medicines and are risk free. I have been familiarized with the testing procedures. I am participating in this study willingly. I have not been forced to do so. I have also been told clearly that I could withdraw from this study without any prejudice.

Date :

Signature :

APPENDIX C

Proforma used for data collection in Normotensive Hypertensive Subjects.

Department of Physiology, S.M.C., Chennai.

Name		Age		Gender	
Date		Time		Group	
Weight (kg)		Height (m)		BMI	
Conditions		Consent		DBD	

Heart Rate variability analysis

Parameter	Supine Rest (256 s)	Standing (256 s)
Mean RR (ms)		
SDNN (ms)		
LF Power (ms^2)		
HF Power ($ms^{2)}$		
Total Power (ms^2)		
LF / HF (ms^2)		
LF nu / HF nu		
NN 50		

BP and HR response to standing

Parameter	SBP	DBP	HR	RPP
Resting Supine				
Upon standing (immediate) (Within 5 seconds)				
2 min after standing				
5 min after standing				
30 / 15 ratio				
Deep breathing difference				
Valsalva Ratio				

BP and HR response to sustained isometric Handgrip

Parameter	SBP	DBP	HR	RPP
Resting				
After 1 min of handgrip				

BP and HR response to cold pressor test

Parameter	SBP	DBP	HR	RPP
Resting				
After 1 min of immersion in cold water				

Signature :

LIST OF ABBREVIATIONS

AV	-	Analysis of Variance
ACE	-	Angiotensin Converting Enzyme
ANFT	-	Autonomic Function Test
ANS	-	Autonomic Nervous System
AV	-	Atrio Ventricular
BP	-	Blood Pressure
BPM	-	Beats Per Minute
BPR	-	Blood Pressure Response
CNS	-	Central Nervous System
CO	-	Cardiac Output
CPT	-	Cold Pressor Test
CV	-	Coefficient of Variation
DBD	-	Deep Breathing Difference
DBP	-	Diastolic Blood Pressure
DMV	-	Dorsal Motor Nucleus of Vagus
ECG	-	Electrocardiogram
FFT	-	Fast Fourier transform
HF	-	High Frequency
HR	-	Heart Rate
HRV	-	Heart Rate Variability
HT	-	Hypertension
IML	-	Inter Mediolateral
IVC	-	Inspiratory Vital Capacity
LF	-	Low Frequency
MI	-	Myocardial Infarction
NE	-	Nor epinephrine
NN50	-	Normal to normal RR interval deviation more than 50 ms.
NTS	-	Nucleus Tract us Solitaries
OHTP	-	Offspring of Hypertensive Parents

ONHTP	-	Offspring of Non Hypertensive Parents
PNS	-	Parasympathetic Nervous Systems
PSD	-	Power Spectral Density
PTI	-	Postural Tachycardia Index
RHR	-	Resting Heart Rate
RPP	-	Rate Pressure Product
RRI	-	RR interval
SA	-	Sino Atrial Node
SBP	-	Systolic Blood Pressure
SD	-	Standard deviation
SDNN	-	Standard Deviation of Average Normal to Normal RR Interval
SIHG	-	Sustained Isometric Handgrip Test
SMC	-	Stanley medical college
SNS	-	Sympathetic Nervous System
TPR	-	Total Peripheral Resistance
TV	-	Tidal Volume
VC	-	Vital Capacity
VLF	-	Very Low Frequency
VLM	-	Ventro Lateral Medulla
VM	-	Valsalva Maneuver
VR	-	Valsalva Ratio
ms^2	-	Milliseconds Squared
r	-	Supine rest
Si	-	Standing immediate
S2	-	Standing 2 minutes
S5	-	Standing 5 minutes